

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Szyperski et al.	)	Examiner:
		)	Y. Gakh
Serial No.	: 10/628,818	)	
		)	Art Unit:
Cnfrm. No.	: 5870	)	1743
		)	
Filed	: July 28, 2003	)	
		)	
For	: PHASE SENSITIVELY-DETECTED REDUCED	)	
	DIMENSIONALITY NUCLEAR MAGNETIC	)	
	RESONANCE SPECTROSCOPY FOR RAPID	)	
	CHEMICAL SHIFT ASSIGNMENT AND	)	
	SECONDARY STRUCTURE DETERMINATION OF	)	
	PROTEINS	)	

DECLARATION OF THOMAS A. SZYPERSKI UNDER 37 C.F.R. § 1.132

**Mail Stop:**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

I, Thomas A. Szyperski, pursuant to 37 C.F.R. § 1.132, declare:

1. I received a Diploma degree in Chemistry from Technical University of Munich, Germany in 1988 and a Dr. Sc. degree in Chemistry from ETH Zurich, Switzerland in 1992.
2. I am currently Professor of Chemistry and Biochemistry, and Director of the UB High-Field NMR Facility at University at Buffalo, The State University of New York, Buffalo, New York. I am also currently Adjunct Senior Researcher at the Hauptman-Woodward Medical Research Institute, Buffalo, New York.
3. As indicated in my attached Curriculum Vitae (Exhibit 1) and list of publications (Exhibit 2), I have authored or co-authored over 100 mostly peer-reviewed professional publications in the fields of nuclear magnetic resonance (NMR) techniques and

structure determination of biological macromolecules using NMR spectroscopy. Since 1999, I have given over 120 invited lectures in these same technical fields (see Exhibit 1).

4. I am an elected member of the American Chemical Society, American Association for the Advancement of Science, and the Gesellschaft Deutscher Chemiker.

5. I am an inventor of the above-identified patent application.

I am presenting this declaration to demonstrate that, contrary to the statement on page 2 of the outstanding office action for the above-identified patent application, none of the NMR experiments disclosed or claimed in U.S. Patent No. 7,141,432 to Szyperski ("Szyperski") disclose or suggest conducting four reduced dimensionality (RD) nuclear magnetic resonance (NMR) experiments on the protein sample, wherein the chemical shift values of  $^1\text{H}$  and  $^{13}\text{C}$  which are encoded in peak pairs of an NMR spectrum are detected in a phase sensitive manner (emphasis added).

6. I am familiar with the claims and disclosure of Szyperski.

7. Claims 1-40 of Szyperski are drawn to a method for obtaining rapid and complete assignments of chemical shift values of  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{15}\text{N}$  of a protein molecule comprising: providing a  $^{15}\text{N}/^{13}\text{C}$ -labeled protein sample; and conducting four RD NMR experiments on the protein sample, where (1) a first experiment is selected from the group consisting of a RD 3D  $\text{H}^{\omega\beta}\text{C}^{\alpha\beta}(\text{CO})\text{NHN}$  NMR experiment, a RD 3D  $\text{HA,CA,CA}(\text{CO}),\text{N,HN}$  NMR experiment, and a RD 3D  $\text{H,C,C}(\text{C-TOCSY-CO}),\text{N,HN}$  NMR experiment for obtaining sequential correlations of chemical shift values; (2) a second experiment is selected from the group consisting of a RD 3D  $\text{HNNCAHA}$  NMR experiment, a RD 3D  $\text{H}^{\omega\beta}\text{C}^{\omega\beta},\text{N,HN}$  NMR experiment, and a RD 3D  $\text{HNN<CO,CA>}$  NMR experiment for obtaining intraresidue correlations of chemical shift values; (3) a third experiment is a RD 3D  $\text{H,C,C,H-COSY}$  NMR experiment for obtaining assignments of sidechain chemical shift values; and (4) a fourth experiment is a RD two-dimensional (2D)  $\text{HB,CB,CG,CD}$ , HD NMR experiment for obtaining assignments of aromatic sidechain chemical shift values.

8. The claims of Szyperski neither disclose nor suggest detection of chemical shift values of  $^1\text{H}$  and  $^{13}\text{C}$  which are encoded in peak pairs of an NMR spectrum in a phase sensitive manner, as required by the claims of the present application (emphasis added).

More specifically, in Szyperski, chemical shifts (also referred to as the 'projected chemical shifts') inferred in RD NMR experiments from the frequency difference of two peaks forming a peak pair arise from cosine modulation (*see, e.g.,* Szyperski at column 4, lines 12-24, column 4, lines 44-55, col. 5, lines 8-22, col. 5, lines 44-57, col. 6, lines 7-18, col. 6, lines 36-47, col. 6, line 65 to col. 7, line 8, and col. 7, lines 23-33). Chemical shifts which are detected using cosine modulation are *not* measured in a phase-sensitive manner. That is, in Szyperski, the frequency difference can relate to a chemical shift being either downfield or up-field to the carrier frequency of the radio-frequency pulse exciting the corresponding spins. In RD NMR, as described in Szyperski, this ambiguity must be resolved by placing the carrier at the edge of the spectral range so that *all* frequency differences correspond to chemical shifts being either downfield or up-field from the carrier frequency. This, however, requires that the spectral width and thus the number of increments that are required to reach a given maximal evolution time has to be increased. In turn, the minimal measurement time is increased by the same amount.

9. Szyperski does teach the generation of certain NMR signals encoding the chemical shift values of  $^{13}\text{C}_{i-1}^{\alpha}$  and  $^{15}\text{N}_i$  (col. 4, lines 8-9),  $^{13}\text{C}_{i-1}^{\alpha\beta}$  and  $^{15}\text{N}_i$  (col. 4, lines 40-42),  $^{13}\text{C}_{i-1}^{\alpha}$ ,  $^{13}\text{C}_{i-1}^{\beta}$ , and  $^{13}\text{C}_i$  (col. 5, lines 4-5),  $^{13}\text{C}_{i-1}^{\alpha}$ ,  $^{13}\text{C}_{i-1}^{\beta}$ , and  $^{15}\text{N}_i$  (col. 5, lines 39-41),  $^{13}\text{C}^m$  and  $^{13}\text{C}^n$  (col. 6, lines 3-5 and 32-33),  $^{13}\text{C}^b$  (col. 6, lines 61-63), and  $^{13}\text{C}^m$  (col. 7, lines 20-21) in a phase sensitive manner. However, this does not relate to detection of chemical shift values of  $^1\text{H}$  and  $^{13}\text{C}$  which are encoded in peak pairs of an NMR spectrum in a phase sensitive manner, as required by the claims of the present invention (emphasis added). In contrast, all teachings in Szyperski relating to chemical shifts of  $^{13}\text{C}$  and  $^1\text{H}$  inferred in RD NMR experiments from the frequency difference of two peaks forming a peak pair arise from cosine modulation. As described above, chemical shifts arising from cosine modulation are not measured in a phase sensitive manner. Szyperski neither attempts to nor achieves the determination of chemical shift values of  $^1\text{H}$  and  $^{13}\text{C}$  which are encoded in peak pairs of an NMR spectrum in a phase sensitive manner.

10. This key drawback of RD NMR as disclosed in Szyperski is resolved by introducing the sine modulation as described in the present patent application. The sine modulation results in an anti-phase peak pair in which either the up-field or the down-field peak is of positive sign (while the other peak of the peak pair is of negative sign). Hence, the

distinction of a peak pair with 'positive peak up-field and negative peak down-field' from a peak pair with 'negative peak up-field and positive peak down-field' enables phase sensitive detection of the chemical shift inferred from the separation of the peaks of the peak pairs generated by sine modulation. The experiments disclosed in the present application represent the fastest possible way to phase-sensitively detect projected chemical shifts encoded in a frequency separation of two peaks.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 12/6/2007

Thomas A. Szypurski  
Thomas A. Szypurski

# **EXHIBIT 1**

## Curriculum Vitae

**Dr. sc. nat ETH Thomas Szyperski**  
**Professor**  
**Director, UB and Roswell Park Cancer Institute NMR facilities**  
**The State University of New York at Buffalo**  
**Chemistry Department**  
 ('cross appointed' in Departments of Biochemistry and Structural Biology)  
**816 Natural Sciences Complex**  
**Buffalo, NY 14260, USA**

Date of birth	December 13, 1963
Place of birth	Berlin, Germany
Nationality	German
Obligatory Military Service	July 1 1982 - September 30, 1983

### Education

Vordiplom Biochemistry, University of Tübingen, Germany	1984
Vordiplom Chemistry, Technical University München, Germany	1985
Diploma Chemistry, Technical University München, Germany	1988
Dr. sc. nat. ETH, ETH Zürich, Switzerland	1992
Mentor: Prof. K. Wüthrich	
Habilitation, ETH Zürich, Switzerland	1998

### Employment History

TU München, Germany	3.1988 - 9.1988
University of Auckland, New Zealand	10.1988 - 2.1989
ETH Zürich, Switzerland	3.1989 - 10.1998
State University of New York, USA	11.1998 –

### **Other Positions**

#### Member of

Operating Committee of the New York Structural Biology Center  
(<http://www.nysbc.org/>)

Executive Committee of the Northeast Structural Genomics Consortium  
(<http://www.nesg.org>)

#### Leader of

NMR Division of the Northeast Structural Genomics Consortium  
(<http://www.nesg.org/>)

### **Awards**

- |                 |   |
|-----------------|---|
| 7.1981 / 7.1982 | Member of the German national team participating at the XIII. and XIV. International Chemistry Olympiads - awarded Silver and Golden Medal, respectively. |
| 5.1993          | 'Medaille der ETH' for outstanding dissertations  |
| 7.1998          | 'Privatdozent' ETH Zürich   |
| 11.1999         | Research Innovation Award of the Research Corporation   |
| 3.2003          | Buck-Whitney Medal of the American Chemical Society   |
| 11.2003         | <i>Scientific American</i> 50 Award for 'Chemistry and Material Sciences'   |
| 4.2006          | Laukien Prize 2006  |
| 5.2007          | SUNY Chancellor's Award for Excellence in Scholarship and Creative Activities   |

### **Honors**

- |                 |   |
|-----------------|---|
| 9.1982 - 9.1988 | Scholar of the 'Studienstiftung des Deutschen Volkes'               |
| 6.1989 - 9.1991 | Scholar of the 'Verband der Chemischen Industrie'                   |
| 5.1999 -        | Adjoined Senior Researcher at 'Hauptman-Woodward Medical Institute' |

**Professional Memberships and Activities**

Member of

American Chemical Society

Gesellschaft Deutscher Chemiker

American Association for the Advancement of Science

Member of

Faculty of 1000

**Professional Service**

Member of

Editorial board of the 'Journal of Structural and Functional Genomics'

Reviewer for scientific journals:

Applied and Environmental Microbiology

Biochemistry

Biopolymers

Bioinformatics Journal

Biotechnology and Bioengineering

Biotechnology Progress

BioTechniques

European Journal of Biochemistry

Journal of the American Chemical Society

Journal of Bacteriology

Journal of Biomolecular NMR

Journal of Magnetic Resonance

Journal of Molecular Biology

Journal of Structural and Functional Genomics

Macromolecules

Magnetic Resonance in Chemistry

Metabolic Engineering

Nature Biotechnology

Structure



**Community Service**

## Reviewer for

NIH: BBCA study section (2000)  
NIH: S10 Instrumentation Panel (2004)  
NIH: NCI site review (2006)  
NSF: Major Research Instrumentation Panel (2001)  
NSF: *Ad Hoc* Reviewer (2002 - 2005)  
NSF: Panel Member (2004, 2005, 2006, 2007)  
Wellcome Trust, United Kingdom (2001; 2003)  
Genome Canada (2004)  
Wiener Wirtschafts-, Forschungs- und Technologiefonds (2005)  
Israel Science Foundation (2005)

**U.S. Patents**

Method of using G-matrix Fourier transformation nuclear magnetic resonance (GFT NMR) spectroscopy for rapid chemical shift assignment and secondary structure determination of proteins.  
US patent number 6.831.459.

Method of using Reduced Dimensionality nuclear magnetic resonance spectroscopy for rapid chemical shift assignment and secondary structure determination of proteins.  
US patent number 7.141.432

## **Invited Lectures (1999 - )**

### **1. USA**

- (1) "NMR Spectroscopy: a Powerful Tool for Life Scientists"  
Biochemistry Department, State University of New York at Buffalo  
Buffalo, New York, February 15, 1999.
- (2) "Sequential Resonance Assignment of Medium-sized  $^{15}\text{N}/^{13}\text{C}$ -Labeled Proteins with Projected 4D Triple Resonance Experiments"  
Varian NMR Users Conference  
Orlando, Florida, March 1, 1999.
- (3) "Indirect Detection of  $^{13}\text{C}$  using 1D and 2D [ $^{13}\text{C}$ ,  $^1\text{H}$ ]-correlation NMR Spectroscopy.  
NIH Symposium:  $^{13}\text{C}$  in Metabolic Research, University of Texas Medical Branch  
Dallas, Texas, May 6, 1999.
- (4) "NMR Spectroscopy in Structural Biology"  
Center of Advanced Research in Molecular Biology and Immunology  
Buffalo, New York, May 18, 1999.
- (5) "NMR Spectroscopy Applied in Structural Biology and Metabolic Research"  
Hauptman-Woodward Medical Research Institute  
Buffalo, New York, June 10, 1999.
- (6) "NMR at SUNYAB"  
1<sup>st</sup> Upstate New York NMR Symposium, Wadsworth Center  
Albany, New York, October 4, 1999.
- (7) "Reduced Dimensionality NMR Experiments for Structural Genomics",  
Symposium NE Structural Genomics Consortium Project Team, Rutgers University,  
Piscataway, New Jersey, November 2, 1999.
- (8) "Structural Biology of the Mitochondrial Origin of Light Strand DNA Replication" Rockefeller  
University, New York, New York, December 13, 1999.
- (9) "Reduced Dimensionality NMR Spectroscopy for Structural Genomics"  
Northeastern Structural Genomics Consortium, Rutgers University,  
Piscataway, New Jersey, December 14, 1999.
- (10) "Novel RD NMR Experiments for Structural Genomics"  
NESG Consortium Workshop,  
Princeton, New Jersey, May 13, 2000.
- (11) "METAFoR by NMR: an Approach Comes of Age"  
Cargill Dow Polymers,  
Minnetonka, Minneapolis, May 24, 2000.

- (12) "Reduced-dimensionality NMR for Structural Genomics"  
Pacific Northwest National Laboratories,  
Redland, Washington, July 29, 2000.
- (13) "Structural Biology in Supercooled Water"  
2<sup>nd</sup> Upstate New York NMR Symposium, Cornell University,  
Ithaca, New York, October 2, 2000.
- (14) "News on RD NMR"  
Cornell Medical School  
New York, New York, November 28, 2000.
- (15) "Reduced-dimensionality NMR spectroscopy"  
RD NMR workshop UB high-field NMR facility and CCR Buffalo,  
Buffalo, New York, December 5, 2000.
- (16) "Structural Genomics by NMR"  
Foster Chemistry Colloquia UB Chemistry Department  
Buffalo, New York, December 8, 2000.
- (17) "Reduced-dimensionality NMR Spectroscopy: An Approach Comes of Age"  
Keystone Symposia, Frontiers of NMR in Molecular Biology  
Big Sky, Montana, January 22, 2001.
- (18) "Bio-NMR at UB: Supercool!"  
Chemistry Department, Youngstown State University  
Youngstown, Ohio, February 9, 2001.
- (19) "Structural Biology in Supercooled Water"  
UB Physics Department Seminar Series  
Buffalo, New York, February 13, 2001.
- (20) "Structural Biology in Supercooled Water"  
Varian NMR Users Conference  
Orlando, Florida, March 9, 2001.
- (21) "Structural Genomics by NMR"  
Center for Computational Research 2000-2001 Colloquium Series  
Buffalo, New York, March 27, 2001.
- (22) "Metabolic Flux Ratio and Bioreaction Network Topology Analysis by NMR"  
Department of Plant Biology Michigan State University  
East Lansing, Michigan, April 25, 2001.
- (23) "Metabolic Flux Ratio and Bioreaction Network Topology Analysis by NMR"  
Microbia Inc.  
Boston, Massachusetts, April 27, 2001.

- (24) "Structural Biology in Supercooled Water"  
3<sup>rd</sup> Upstate New York NMR meeting  
Rochester, New York, October 15, 2001.
- (25) "Metabolic Profiling by NMR"  
Industrial Associates Program New Jersey  
Princeton, New Jersey, October 16, 2001.
- (26) "RD NMR for Structural Genomics"  
Bristol-Myers-Squibb  
Princeton, New Jersey, October 17, 2001.
- (27) "Structural Biology in Supercooled Water"  
NJ American Chemical Society NMR Topic Group  
Princeton, New Jersey, October 17, 2001.
- (28) "Metabolic Profiling by NMR" Metabolic Profiling: Pathways in Discovery Cambridge  
Healthtech Institute's Premier Conference  
Chapel Hill, North Carolina, December 4, 2001.
- (29) "Structural Genomics by NMR"  
NIEHS  
Chapel Hill, North Carolina, December 5, 2001.
- (30) "NMR at UB"  
Kent State University  
Kent, Ohio, January 31, 2002.
- (31) "NMR Sample Preparation for High-throughput Structure Determination"  
NIH-PSI workshop  
Bethesda, Maryland, March 7, 2002.
- (32) "NMR-based structural genomics"  
Buffalo-Niagara Post-genomic Research Conference  
Buffalo, New York, May 15, 2002.
- (33) "New NMR methods for Structural Genomics"  
NESG consortium, Annual Meeting Center for Advanced Biotechnology and Medicine  
Piscataway, New Jersey, June 10, 2002.
- (34) "News on RD NMR"  
NIH workshop University of Wisconsin  
Madison, Wisconsin, June 21, 2002.
- (35) "Metabolic Profiling: New Insights"  
2002 Annual Meeting of the Society for Industrial Microbiology  
Philadelphia, Pennsylvania, August 11-15, 2002.

- (36) "NMR Methodology for High-Throughput Protein Resonance Assignment"  
Biotechnology Forum  
Buffalo, New York, October 22, 2002.
- (37) "NMR in the post-genomic era"  
Juniata College  
Huntingdon, Pennsylvania, November 19, 2002.
- (38) "GFT NMR Spectroscopy"  
Rutgers University  
Piscataway, New Jersey, December 11, 2002.
- (39) 'NMR spectroscopy for structural genomics'  
Rutgers University  
Piscataway, New Jersey, January 22, 2002.
- (40) 'GFT NMR, a new approach to rapidly obtain precise high-dimensional NMR spectral information'  
Keystone Symposium, Frontiers in Structural Biology  
Taos, New Mexico, February 8, 2003.
- (41) 'NMR methodology for structural genomics'  
Rutgers University  
Piscataway, New Jersey, February 13, 2003.
- (42) 'NMR in the postgenomic era'  
Roswell Park Cancer Institute  
Buffalo, New York, February 24, 2003.
- (43) 'NMR-based Structural Genomics: New Methods and Perspectives'  
New York State Proteomics Symposium  
Syracuse, New York, March 17, 2003.
- (44) 'GFT NMR: rapid and precise NMR data collection'  
Varian Users Meeting  
Savannah, Georgia, March 29, 2003.
- (45) 'Implementation of GFT NMR experiments'  
Bruker Users Meeting  
Savannah, Georgia, March 29, 2003.
- (46) 'GFT NMR Spectroscopy: Theory and Applications'  
44<sup>th</sup> Experimental NMR Conference  
Savannah, Georgia, April 4, 2003.
- (47) 'NMR Methodology for Structural Genomics'  
Buffalo Excellence in Biological Sciences Seminar Series  
Buffalo, New York, May 15, 2003.

- (48) 'RD and GFT NMR: new NMR methods for rapid protein structure determination'  
Middle Atlantic Regional Meeting of the ACS  
Princeton, New York, June 11, 2003.
- (49) 'NMR for structural biology and metabolic profiling'  
Northeastern Regional Meeting of the ACS  
Saratoga Springs, New York, June 18, 2003.
- (50) 'Profiling Yeast Metabolism by NMR'  
National meeting of the American Chemical Society  
New York, New York, September 12, 2003.
- (51) 'NMR at UB: Structural Genomics and Metabolic Flux Profiling'  
Seminar Series  
Roswell Park Cancer Institute  
Buffalo, New York, February 20, 2004
- (52) 'GFT NMR News'  
45<sup>th</sup> Experimental NMR Conference,  
Asilomar, California, April 23, 2004.
- (53) "NMR Methods Enabling Rapid Data Collection"  
EMSL meeting 2004, Pacific Northwest National Laboratories  
Redland, Washington, June 16, 2004.
- (54) 'Rapid Acquisition of Multidimensional NMR data'  
Gordon Research Conference in Stereochemistry  
Salve Regina University  
Newport, Rhode Island, June 21, 2004
- (55) 'GFT NMR – Toward HTP NMR Structure Determination'  
Departmental Lecture Series, Chemistry Department  
University of Rochester  
Rochester, New York, October 27, 2004
- (56) 'Rapid Sampling of NMR Data'  
International Conference on Structural Genomics  
Washington, DC, November 20, 2004
- (57) 'NMR Methodology for Structural Genomics'  
NESG Methodology Retreat  
Rutgers University  
New Brunswick, NJ, March 13, 2005
- (58) 'Fast Acquisition of Multidimensional NMR Data: Implications for Structural Genomics'  
Departmental Lecture Series, Chemistry Department  
Fayetteville, Arkansas, March 28, 2005

- (59) 'GFT NMR – Rapid Protein NMR Data Collection for Structural Genomics'  
Departmental Lecture Series, Chemistry Department  
Seattle, Washington, March 30, 2005
- (60) 'New Methodology for PSI-2: GFT NOESY and G2FT NMR  
NESG NMR Division Workshop  
Buffalo, New York, May 24, 2005
- (61) 'Where do we stand on HTP NMR Structure Determination'  
NESG Retreat  
Princeton, New Jersey, June 21, 2005
- (62) 'GFT NMR-based Structural Genomics'  
Keystone Symposia, Frontiers in Structural Biology  
Keystone, Colorado, January 31, 2006
- (63) 'High-throughput Protein Structure Determination by NMR: New Methodology & Impact on  
Structural Biology'  
Amgen Inc.  
Thousand Oaks, California, March 17, 2006
- (64) 'GFT Projection NMR Spectroscopy: Principles and Applications'  
Amgen Inc.  
Thousand Oaks, California, March 17, 2006
- (65) 'GFT NMR based Structural Biology'  
Departmental Lecture Series, Physics Department  
Washington University  
St. Louis, Missouri, April 3, 2006
- (66) 'G-matrix Fourier Transform Projection NMR Spectroscopy'  
Laukien Prize Lecture  
Experimental NMR Conference  
Asilomar, California, April 24, 2006
- (67) 'GFT Projection NMR'  
Cleveland Center for Structural Biology NMR Symposium  
Cleveland, Ohio, May 13, 2006
- (68) 'G-matrix Fourier Transform Projection NMR: Theory and Application'  
Workshop on 'NMR data Collection and Analysis'  
University of Wisconsin  
Madison, WI, June 6, 2006
- (69) 'NMR-based structural genomics'  
Canisius College, Chemistry Department  
Buffalo, NY, September 8, 2006

(70) 'Methodology for rapid NMR data collection'  
 Eastern Analytical Session  
 Somerset, NJ, November 13, 2006

(71) 'GFT Projection NMR: Application in Structural Biology'  
 Departmental lecture series, Chemistry Department  
 University of Illinois at Urbana-Champaign  
 Urbana-Champaign, IL, November 29, 2006

(72) 'Structural Genomics in an 'omics'-world'  
 Metabonomics Research Day,  
 University at Buffalo,  
 Buffalo, NY, January 8, 2007

(73) 'GFT NMR for membrane proteins'  
 Retreat, New York Center on Membrane Protein Structure  
 New York Structural Biology Center,  
 New York, NY, March 14, 2007

(74) 'Role of GFT Projection NMR for NESG'  
 CCPN workshop  
 Rutgers University  
 New Brunswick, NJ, March 15, 2007

(75) 'Structural Genomics in an 'omics'-world'  
 Seminar Series  
 Department of Gynecology  
 University at Buffalo, April 25, 2007

(76) 'The NESG NMR Program'  
 NESGC NIH site visit  
 Rutgers University  
 New Brunswick, NJ, May 4, 2007

(77) 'GFT Projection NMR Spectroscopy'  
 SECNMR  
 Web-seminar, September 26, 2007

(78) 'Where do we stand for Projection NMR spectroscopy for HTP protein structure determination?'  
 Amgen Inc.  
 Thousand Oaks, California, October 6, 2007

(79) 'Where do we stand on Projection NMR Spectroscopy'  
 Upstate NY NMR Symposium  
 SUNY College of ESC  
 Syracuse, NY, October 12, 2007



(80) 'NMR can be entertaining'

New Jersey NMR topical group

Somerset, NJ, November 12, 2007

(81) 'GFT NMR Spectroscopy: application for membrane protein structure determination'

New York Structural Biology Center

New York, NY, November 30, 2007

## 2. International

- (1) "Synergy of  $^{13}\text{C}$ -labeling of Amino Acids and Metabolic Flux Balancing- a Novel Approach to Support Process Design in Biotechnology"  
International Conference on Magnetic Resonance in Biological Systems,  
Tokyo, Japan, August 27, 1998.
- (2) "Exploration of Central Carbon Metabolism using Biosynthetic Fractional  $^{13}\text{C}$ -Labeling and Two-dimensional NMR Spectroscopy"  
Metabolic Engineering Conference II  
Elmau, Germany, October 16, 1998.
- (3) "METAFoR by NMR Analysis for Biotechnology Research"  
ETH Zürich  
Zürich, Switzerland, September 2, 1999.
- (4) "NMR Structure of a Chimeric Hybrid Duplex Formed During Initiation of HIV-1 Reverse Transcription"  
4th Annual Workshop "Structure-Function Analysis of Drug Resistant HIV-RT"  
Rome, Italy, November 12, 1999.
- (5) "Neuere Erkenntnisse über lebende Systeme mittels NMR Spektroskopie"  
Universität Düsseldorf  
Düsseldorf, Germany, January 10, 2000.
- (6) " $^{13}\text{C}$ -labeling Experiments in Support of Biotechnology Research"  
Swiss National Science Foundation Symposium: The Swiss Priority Project Biotechnology,  
ETH Zürich,  
Zürich, Switzerland, March 23, 2000.
- (7) "Towards Structural Biology in Supercooled Water. Implications for the Structure of FluA"  
Technische Universität München  
München, Germany, March 29, 2000.
- (8) "Kernresonanzspektroskopie - faszinierende neue Möglichkeiten zur Ergründung biomolekularer Vorgänge"  
Universität Siegen  
Siegen, Germany, July 4, 2000.
- (9) "Reduced Dimensionality NMR for Structural Genomics"  
Protein Engineering Network of Centers of Excellence  
Toronto, Canada, October 19, 2000.
- (10) "Rapid NMR assignment of Proteins for High-throughput Structure Determination"  
1<sup>st</sup> International Conference on Structural Genomics (ICSG) 2000  
Yokohama, Japan, November 3, 2000.
- (11) "Structural Biology in Supercooled Water"  
NMR in Molecular Biology, European Science Foundation (ESF)  
Karrebaksmünde, Denmark, June 11, 2001.

- (12) "Structural Genomics by NMR"  
Institute of Biotechnology  
Vilnius, Lithuania, October 5, 2001.
- (13) "Structural Biology in Supercooled Water"  
Institute of Biotechnology  
Vilnius, Lithuania, August 6, 2002.
- (14) "Structural Biology in Supercooled Water"  
20<sup>th</sup> International Conference on MR in Biological Systems  
Toronto, Canada, August 27, 2002.
- (15) "Flux Information from NMR Data"  
FEBS Course "Advanced Technologies For Metabolic Engineering in Biotechnology and Medicine"  
Lisbon, Portugal, September 7-14, 2002.
- (16) "NMR for Metabolic Profiling: New Insights"  
FEBS Course "Advanced Technologies For Metabolic Engineering in Biotechnology and Medicine"  
Lisbon, Portugal, September 7-14, 2002.
- (17) 'GFT NMR'  
Biochemistry Department, University of Toronto  
Toronto, Canada, February 27, 2003.
- (18) 'NMR in high-throughput: Structural Genomics and Metabolic Flux Profiling'  
AstraZeneca Biotechnology Seminar Series  
Mississauga, Canada, February 27, 2003.
- (19) 'Strukturelle Genomik: Semiempirische Lösung des Proteinfaltungsproblems?'  
Seminar Series of the 'Bayreuther Zentrum für Molekulare Biowissenschaften'  
Bayreuth, Germany, April 25, 2003.
- (20) 'GFT NMR spectroscopy: Rethinking Multidimensional Data Acquisition'  
16<sup>th</sup> International Conference on NMR Spectroscopy  
Cambridge, UK, July 1, 2003.
- (21) 'GFT NMR for rapid NMR data acquisition'  
Jahrestagung der Fachgruppe Resonanzspektroskopie (GDCh)  
Leipzig, Germany, October 2, 2003.
- (22) 'Structural Genomics by NMR: Novel Methods and Insights'  
3<sup>rd</sup> NCCR Symposium on New Trends in Structural Biology  
Switzerland, Zürich, November 15, 2003.
- (23) 'GFT NMR, Progress for Rapid NMR Data Collection'  
21<sup>st</sup> International Conference on Magnetic Resonance in Biological Systems  
Hyderabad, India, January 2005

- (24) 'GFT NMR Based Protein Structure Determination in High-Throughput'  
Keystone Symposium, Frontiers in Structural Biology  
Banff, Canada, February 1, 2005
- (25) 'Strukturelle Genomik: Revolution in Grundlagenforschung und  
Medikamentenentwicklung'  
Virtoweb, Support of IT for Biotech  
Bochum, Germany, February 18, 2005
- (26) 'Studies of the M.HhaI – DNA system'  
Institute for Biotechnology  
Vilnius, Lithuania, August 18, 2005
- (27) 'Protocol for NMR-based Structural Proteomics'  
HUPO 4th Annual World Congress  
Munich, Germany, August 29, 2005
- (28) 'NMR-based Structural Genomics'  
Chemistry Department Lecture Series  
Reykjavik, Iceland, October 7, 2005
- (29) 'Methodology for NMR-based Structural Genomics'  
NMR Department, Max-Planck Institute for Biophysical Chemistry  
Göttingen, Germany, October 24, 2005
- (30) 'GFT Projection NMR Spectroscopy'  
University of Halle, Physics Lecture Series  
Halle, Germany, October 27, 2005
- (31) 'NMR for Structural Genomics'  
SCAI of the Fraunhofer Gesellschaft  
Bonn, Germany, November 9, 2005
- (32) 'GFT NMR for structural and dynamic studies of proteins in solution '  
7th Igler NMR-symposium  
Oberurg, Austria, February 14, 2006
- (33) 'NMR studies of M.HhaI-DNA complexes'  
Institute for Biotechnology  
Vilnius, Lithuania, May 29, 2006
- (34) 'High-throughput protein structure determination for NMR-based structural genomics'  
RWTH Aachen, Chemistry Department  
Aachen, Germany, September 28, 2006
- (35) 'G-matrix Fourier Transform projection NMR spectroscopy'  
RIKEN NMR Center  
Yokohama, Japan, October 21, 2006

(36) 'GFT NMR data acquisition, processing and analysis'  
RIKEN NMR center  
Yokohama, Japan, October 21, 2006

(37) 'GFT projection NMR spectroscopy'  
International Conference on Structural Genomics  
Beijing, China, October 24, 2006

(38) 'Theory and Application of GFT NMR'  
Beijing NMR center, Beijing University  
Beijing, China, October 28, 2006

(39) 'Theory and Application of GFT NMR'  
University of Science and Technology  
Hefei, China, November 2, 2006

(40) 'Structural Genomics in an 'omics'-world'  
University of Campinas  
Campinas, Brazil, February 12, 2007

(41) 'GFT Projection NMR for high-throughput protein structure determination'  
II Structural Biology Workshop of the LNLS  
Campinas, Brazil, February 14, 2007

(42) 'GFT Projection NMR: Theory and Application'  
Hong Kong University of Science and Technology  
Hong Kong, March 5, 2007

(43) 'Structural genomics in an 'omics'-world'  
SCAI of the Fraunhofer Gesellschaft  
Bonn, Germany, May 7, 2007

(44) 'Where do we stand on projection NMR?'  
Chianti Workshop  
Vallombrosa, Italy, June 5, 2007

(45) 'Structural genomics in an 'omics'-world'  
University of Florence  
Florence, Italy, June 8, 2007

## **EXHIBIT 2**

1. Szyperski, T. and Schwerdtfeger, P. (1989) On the Stability of Trioxo(h<sup>5</sup>-Cyclopentadienyl) Compounds of Manganese, Technetium and Rhenium: An *ab initio* SCF Study. *Angew. Chem. Int. Ed. Engl.* **28**, 1228-1231.
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